II. THE REGULATED COMMUNITY

This chapter describes the section of the biotechnology industry that produces and/or uses microorganisms falling under the jurisdiction of the Toxic Substances Control Act (TSCA). The chapter is organized into 4 sections as follows:

- Section A discusses biotechnology applications regulated under TSCA;
- Section B provides an overview of the TSCA biotechnology industry and describes companies involved in TSCA microbial biotechnology activities;
- Section C describes the various application areas; and
- Section D discusses university research.

Much of the industry currently uses only naturally occurring microorganisms in R&D and commercial activities. These organisms are implicitly included on the TSCA Inventory under current policy and are not affected by the rule. The entire industry is described here, however, because applications now using naturally occurring microorganisms may eventually make use of intergeneric microorganisms affected by the rule.

A. Overview of Microbial Applications Subject to TSCA

The microorganisms potentially affected by the rule are those for which the corresponding chemical use would be subject to TSCA jurisdiction. By statute, the Toxic Substances Control Act (TSCA)* regulates all chemical applications not specifically exempted in the Act. Language in the Act has been interpreted to include living microorganisms (i.e., microscopic living cells such as bacteria, fungi, protozoa, microscopic algae, and viruses).**

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15 U.S.C. §§2601 et seq.

TSCA also covers other biologically derived substances, such as chemicals extracted from plants or animals. However, these applications are not affected by the rule because they are subject to the requirements of 40 CFR Part 720.

Table II-1 lists the excluded applications -- mainly food, drugs, cosmetics, animal drugs and feed additives, and pesticides. Table II-2 lists the leading applications subject to TSCA jurisdiction, such as the production of enzymes for use in laundry detergents, production of fuel ethanol, use in nitrogen fixation for legumes, and use in waste treatment.

B. Biotechnology Industry Overview

This section presents an overview of various components of the biotechnology industry. The section is organized into 4 parts as follows:

- Part 1 presents the technologies, techniques, and applications within the industry;
- Part 2 describes the 1988 EPA survey of TSCA biotechnology firms (ICF 1988);
- Part 3 presents the magnitude of TSCA microbial markets; and
- Part 4 presents the types of companies involved in TSCA microbial applications.

1. The Technologies

Biotechnology involves the use of living organisms, such as bacteria, yeast, viruses and other microorganisms, plants, and animals, to produce desired products. The development of microorganisms with desirable properties can be accomplished using various biotechnological techniques involving the selection and manipulation of DNA (deoxyribonucleic acid, the molecule that carries genetic information). One common approach involves deliberate mutation using chemicals or ultraviolet light. Organisms that demonstrate desirable properties are isolated from the culture and propagated separately.

Alternatively, instead of deliberately mutating cells, researchers may merely select the most promising cells from heterogeneous cell populations and grow them for later use. For example, they may obtain a soil sample from a

Table II-1. Applications Not Subject to TSCA

The following applications would be excluded under TSCA Sections 3 and 22:

- Human medicines, cosmetics, medical diagnostics, medical devices, and intermediates used in their production;
- Food, flavorings, additives, beer and other beverages, and their intermediates;
- Animal drugs, feed additives, silage inoculants, and their intermediates;
- Pesticides (i.e., microorganisms used as pesticides). These are regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act. However, intermediates used in the production of these substances come under TSCA jurisdiction;
- National defense activities for which the President has granted a waiver.

Table II-2. Examples of Microbial Applications Under TSCA

- Microbial production of enzymes used in household detergents;
- Microbial production of enzymes for ethanol production, leather tanning, paper manufacturing, and textile manufacture;
- Microbial production of other specialty chemicals such as pesticide intermediates or degreasing agents;
- Microbial production of commodity chemicals such as fuel ethanol, xanthan gum for oil recovery, and citric acid for use in detergents or other TSCA applications;
- Microorganisms or microbial products used for routine non-R&D analysis such as detection of water contaminants (R&D reagents also fall under TSCA jurisdiction, but are exempt from reporting so long as the microorganism meets specific requirements for containment, documentation, and risk notification);
- Microorganisms added to waste treatment facilities or contaminated sites (such as Superfund sites) to degrade sewage and toxic wastes;
- Microorganisms used for nitrogen fixation are added to alfalfa, soybean, and other legume crops in order to promote plant growth, and, microalgal soil conditioners for farming;
- Microorganisms used to help leach copper and other metals out of ore during mining operations; and
- Microorganisms injected into oil wells to enhance oil recovery (no large scale applications have been attempted).

contaminated site, and then select cells within the sample that are naturally successful at degrading toxic chemicals.

Other methods involve combining genetic material from different organisms. Microorganisms are called "intergeneric" if the source organisms are in different genera, and "intrageneric" if the source organisms are from the same genus. Methods of transferring genetic material from one cell to another include physiological processes such as conjugation (cell mating), transduction (using viruses as vectors), or transformation (the cell takes up naked DNA directly from the culture media).* The recombinant DNA technique, in which enzymes are used as chemical scissors to cut and splice DNA in precise ways, can be used with these techniques to create combinations of genetic material. Some of the biotechnological techniques applicable to microorganisms are summarized in Table II-3.

2. 1988 EPA Survey of TSCA Biotechnology Firms

To better characterize the segment of the biotechnology industry that is potentially subject to TSCA, EPA commissioned a survey in 1988 which was conducted by ICF Incorporated. The survey results reflect the responses of 72 companies identified as working with microorganisms in TSCA-related market areas. Universities were not surveyed. The major topics covered in the survey included:

- Financial Information, including total annual budget, sources of funds, overall R&D budget, proportion of R&D budget allocated to biotechnology and to TSCA-related products;
- Market Information, categorizing a company's TSCA products by end use market area;
- Product Characterization, noting the specific type of genetic manipulations, level of containment, and stage of development;

* Note that both intergeneric and intrageneric changes are covered by the rule, but other physical/chemical methods of change are not.

Table II-3. Biotechnological Techniques

- Selection of naturally occurring organisms involves no deliberate genetic manipulation. The most promising microorganisms are selected from a heterogeneous cell population and cultured.

- Mutagenesis. Microorganisms are intentionally mutated through exposure to UV light, mutagenic chemicals, etc. Exposure to mutagens speeds up the natural mutation process. The most promising microorganisms are then selected and grown.

- Conjugation, transduction, transformation. DNA is transferred from one cell to another through "mating," through the use of viruses as transportation vectors, or by diffusion through a liquid medium.

- Recombinant DNA is defined by NIH as (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above.

- Other advanced techniques for combining DNA from two or more microorganisms, such as cell fusion, microinjection (injecting genetic material into a host microorganism), microprojectile processes, and electroporation (introducing large molecules into cells by subjecting cell to current, thus inducing changes in the permeability of the cell membrane).

- New Uses, capturing a company's impressions of possible future applications and markets;

- Institutional Biosafety Committees (IBCs), including the size, labor requirements, and liability insurance needs; and

- Field Trials, determining the number of tests per microorganism and the number of microorganisms tested to develop one commercial product.

3. The Magnitude of TSCA Microbial Markets

It is difficult to comprehensively describe or accurately estimate the share of the biotechnology market potentially affected by the rule. One reason for this difficulty is that TSCA is a "gap filling" statute; it has jurisdiction over all applications not specifically exempted in the statute, rather than a well defined set of applications. A second reason is that most market studies do not specifically examine TSCA biotechnology applications, so that good data are not available concerning the magnitude of TSCA microbial activity.

Although unable to quantify the exact magnitude of TSCA microbial activity, the Agency believes that activities involving microorganisms in areas subject to TSCA comprise a modest share of overall biotechnology activity. Most biotechnology research and commercial production appears to focus on applications exempt from TSCA -- medical, food, beverages, and microbial pesticides -- or involves manipulations of plant and animals rather than microorganisms. According to one estimate, there are over 1,000 companies pursuing biotechnology activities in the U.S. (Burrill 1989). Of these, the Agency has identified about 130 firms as "probably" being involved in R&D or commercial production of microorganisms in applications that fall

under TSCA jurisdiction.* However, many of these use naturally occurring microorganisms, and so would not be affected by the rule.

Only a few companies have submitted Premanufacture Notices (PMNs) for microorganisms used in applications subject to TSCA, even though PMN reporting has been mandatory for new intergeneric microorganisms in general commercial use since 1986.

Figures II-1 and II-2, based on R&D spending data from a report by the Office of Technology Assessment and on EPA survey data and judgment, suggests that TSCA microbial activities represent a relatively small portion of the estimated R&D spending in biotechnology. Total R&D spending in biotechnology has been estimated at $1.8 billion in 1988. EPA has estimated the TSCA share at roughly 7 to 13 percent (ICF 1988, see Appendix A; Burrill 1989).

There is uncertainty concerning this estimate, as well as the estimates of industry growth. One industry survey with information from 480 biotechnology companies, predicts "tenfold growth in sales within 5 years and 25-fold growth within 10 years" (Burrill 1989). While it is not known whether TSCA applications will grow at this pace over the next few years, numerous TSCA applications of microorganisms that would be considered new under this rule are being investigated in university, industry, and government laboratories and eventually TSCA microbial applications are likely to take on commercial importance. Most sources familiar with the TSCA markets, however, do not expect a major acceleration in the next 5 years and instead expect the

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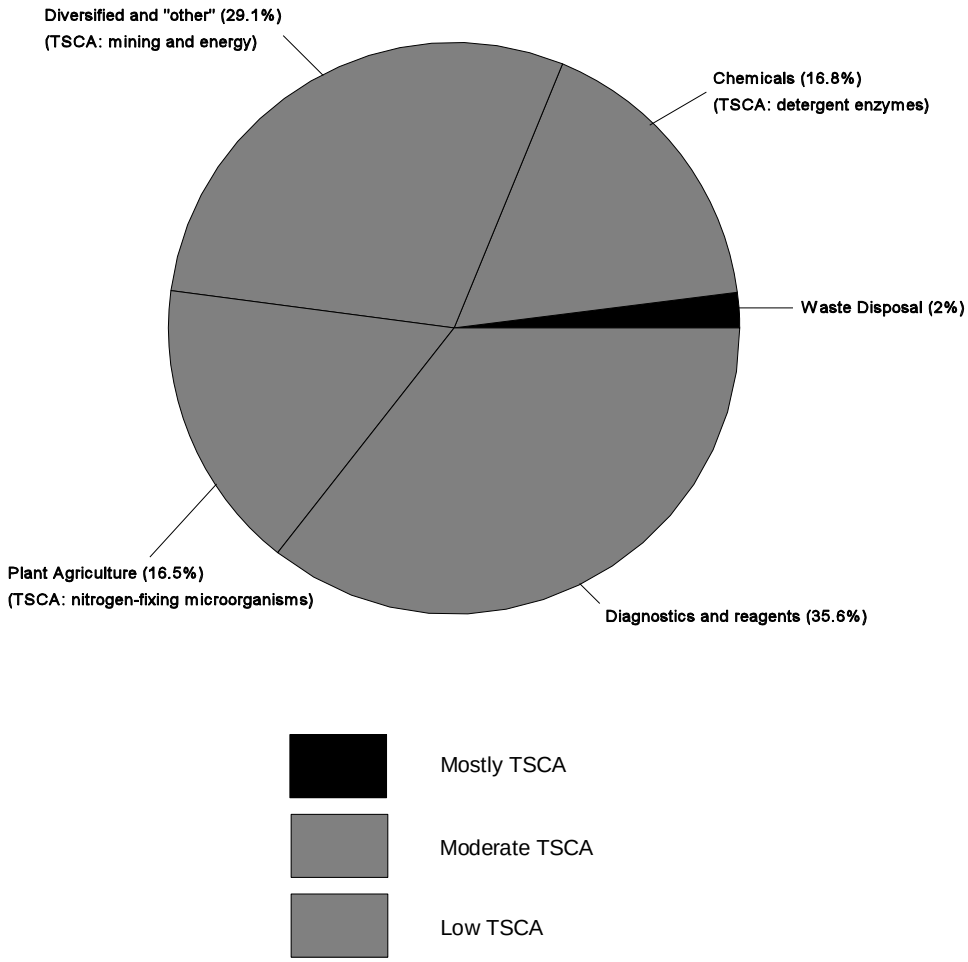
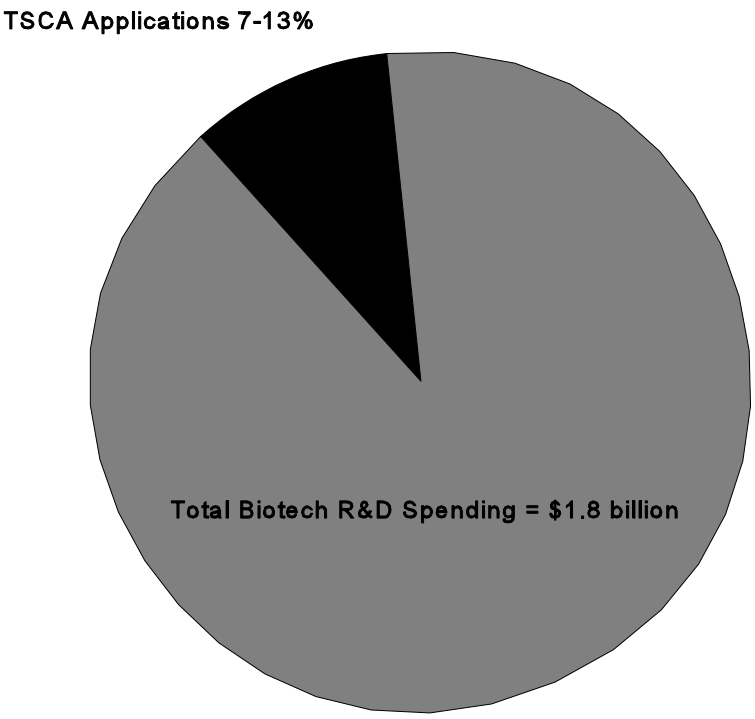
* 72 companies were confirmed as engaging in TSCA microbial activities in the 1988 survey conducted for the Agency by ICF Incorporated described in Appendix A (ICF 1988). Additional companies were identified as probably being involved through trade publications and other public sources. Additional firms have been identified as possibly being involved. In October of 1991, an updated version of one of the sources used to identify companies in TSCA market areas was reviewed. The number of companies that the source identified as potentially working in these areas was not significantly different from the number in 1988 (GEN 1991).

Figure II-1.
U.S. R&D Spending on Biotechnology



Source: EPA estimates based on OTA 1989, ICF 1988, and industry publications

Figure II-2
TSCA R&D Spending as a Fraction of Overall Biotech R&D Spending



Source: EPA estimates based on OTA 1989, ICF 1988, and industry publication

current trends to continue (IBA 1991). Between 1988 and the present, trends in R&D spending indicate significant growth for biotechnology spending. For example, the federal government spent approximately $4 billion on biotechnology grants in 1995, compared to $1.8 billion spent in 1988 on total biotechnology R&D (Vermont 1995). However, TSCA activities as a percentage of R&D spending has decreased to approximately 5% (McKinney 1995).

4. Types of Companies with TSCA Microbial Applications

For convenience, this analysis refers to the TSCA microbial biotechnology "industry." However, the activities discussed actually occur in a number of different industries. Most companies working in TSCA microbial areas fall into the following broad groups (Appendix A).*

- Major U.S. and foreign-owned companies in the chemical, drug, oil, food, and other industries. TSCA microbial activities are usually very small relative to the overall company size. Examples include CPC International, Eastman Kodak, General Electric, and Monsanto.

- Foreign-based companies that are leaders in the world industrial enzyme market. Examples are: Novo-Nordisk (Denmark) and Gist-Brocades (Netherlands) (Simpson 1990).

- Small and medium-sized companies that are considered to be "biotechnology companies." An example is Research Seeds International, which has submitted voluntary PMNs to EPA for field experiments using nitrogen fixation microorganisms. These companies often focus on non-TSCA areas such as medical and animal health, plant agriculture, or food, with TSCA microbial applications accounting for only a small aspect of their business.

* Information about individual companies was based on public sources including PMN submissions obtained from the EPA public docket, company financial reports and product literature, industry directories, and trade periodicals. Responses to the 1988 survey conducted for the Agency by ICF Incorporated were confidential; only aggregate survey data is presented in this RIA (See Appendix A).

- Small and medium-sized companies supplying microbial inoculants for waste treatment and/or agricultural applications. TSCA biotechnology applications are likely to be a major market area for these companies. However, most are working only with naturally occurring microorganisms, and so may not be affected by the rule.*

Other organizations involved in TSCA biotechnology include research institutions such as the Electric Power Research Institute, many universities, and Federal laboratories.

In annual sales, the TSCA portion of the biotechnology industry appears to divide sharply between large and small firms. As Figure II-3 shows, roughly half of the companies providing sales data in the survey (25 out of 46) had sales of $40 million or more, and many were very large companies with sales of over $500 million. Most of the remaining 21 had sales of under $10million, with relatively few near the $40 million cutoff used to define small businesses under TSCA regulations (40 CFR 704.3).**

C. University Research

Financial interactions between academia and industry are becoming more prevalent. Thus, under the current interpretation of "commercial purposes," some academic institutions could be subject to the rule (Some research occurring on university campuses would have been captured regardless of which "commercial purposes" option had been chosen. However, the interpretation EPA has chosen to implement results in fewer R&D activities on university campuses being subject to TSCA Section 5). This section provides an overview of university-industry partnerships and of university applications potentially affected by the rule.

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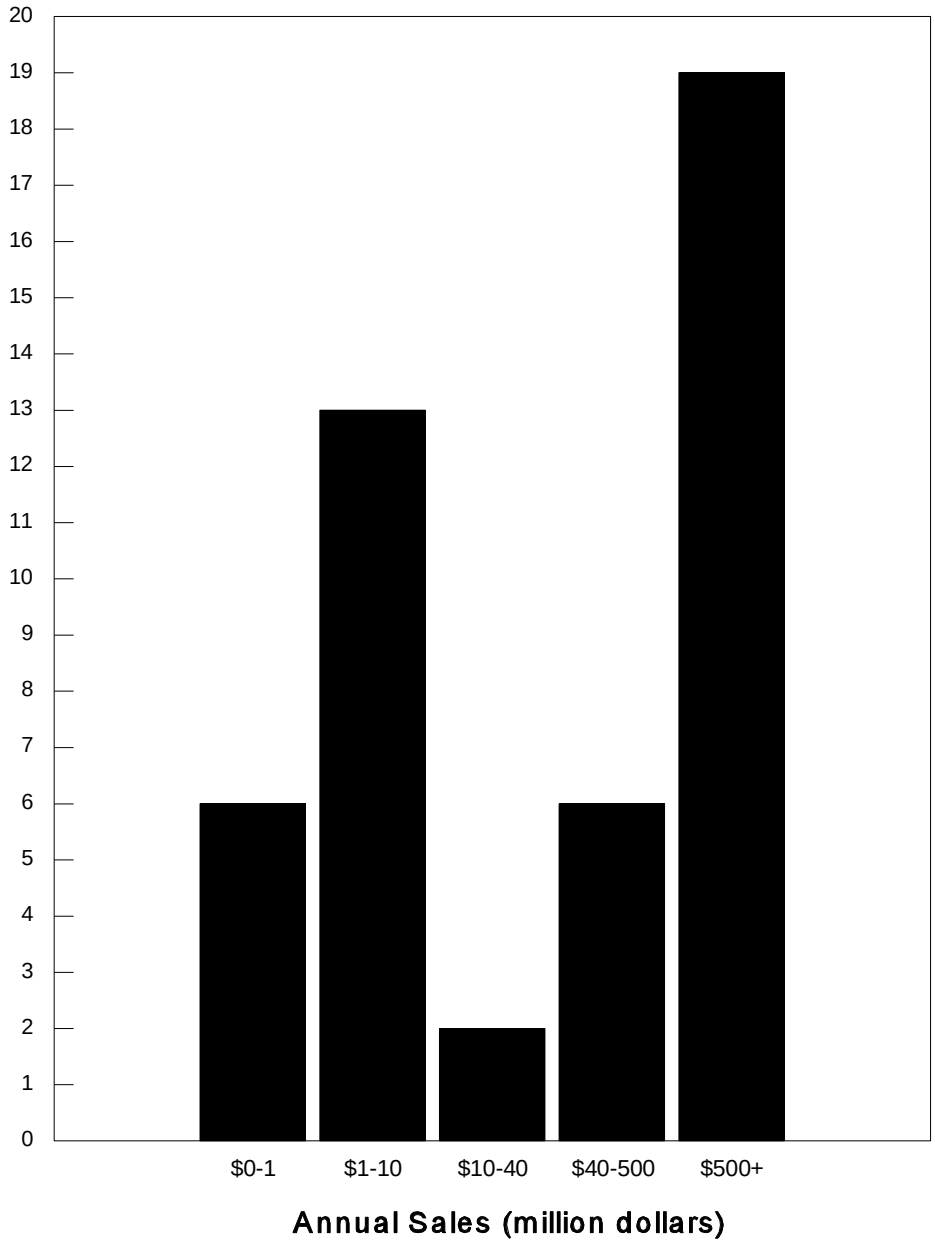
* A related sector is companies that provide biological waste treatment services, including remediation of toxic waste sites using naturally occurring microorganisms (HMCRI 1989).

** Implications of the proposed rule for small businesses are discussed in Chapter VIII.

Figure II-3. Annual Sales



Note: Data represents responses of 46 companies.

Source: ICF 1988.

1. University Biotechnology Activities

Universities perform a significant amount of the nation's biotechnology research. According to the Office of Technology Assessment, the federal government spent an estimated $1.35 billion on biotechnology research at universities in FY 1987 (Cornish 1989). In 1987, NIH provided at least $465 million for recombinant DNA research projects at academic institutions (NIH 1988). Additionally, a substantial amount of funding came from industry. According to the one study, 46% of biotechnology companies supported research at universities in 1984 amounting to an estimated total of $120.7 million in research funds (Blumenthal 1986).

2. University-Industry Partnerships

In 1984, the average Fortune 500 biotechnology company spent $1.1 million on university-directed research and 76% of university laboratories reported receiving industry funding for biotechnology R&D (Cornish 1989). The resulting university-industry research relationships are pervasive. They range from unrestricted grants to contracts that give corporations specific rights to university technology, including the right to license patents owned by the university and the right to preview academic articles for patentable results. An agreement may involve a single company, or it may involve multiple corporate sponsors, sometimes with state and/or federal funding as well. It may be limited to a year or two and confined to a specific project, or it may allow the corporate sponsor to broadly tap into the results of university biological research over periods of as long as ten or more years (Rawie 1988).

Many of the best-known agreements have emphasized medical applications, but some have covered applications relevant to TSCA. For example, the University of Wisconsin at Madison formed a biopulping consortium to help

maintain the state's pulp and paper industries (Biotechnology 1989). In addition, agreements that give industry access to basic molecular biology research may lead to products in a wide variety of fields, including TSCA applications.

3. Potential University Submissions in TSCA Market Areas

Universities were not included in the ICF 1988 survey, and the Agency has not developed quantitative information on the amount and nature of university microbial research in TSCA applications. It has been determined, however, that 306 universities are potentially involved in biotechnology research. This estimate is based on the numbers of universities requesting grants from NIH for rDNA research. Assuming that the university community is just as likely to perform biotechnology research as the industrial community with whom they have contracts, the number of submissions from the university group, as a whole, is expected to be equal to the number of industrial applications for the same purposes (ICF 1988, ETD estimates).